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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,985	12/19/2001	Carine Capiau	B45182	2966

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/936,985	CAPIAU ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9, 11, 12 and 14-15* is/are pending in the application.

4a) Of the above claim(s) *12 and 14-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's response to the Restriction requirement filed July 30, 2002 is acknowledged. Applicant's election of Group I with traverse claims 1-9 and 11 and species F, CbpA is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the restriction requirement is deemed to be proper and is therefore made FINAL. Claims 12 and 14-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for at least one *Streptococcus pneumoniae* polysaccharide protein antigen and at least one *Streptococcus pneumoniae* protein antigen, does not reasonably provide enablement for immunologically functional variants or transmembrane deletion variants thereof.

Claims 1-9 and 11 are drawn to an immunogenic composition comprising at least one *Streptococcus pnuemoniae* polysaccharide antigen, at least one *Streptococcus pneumoniae* protein antigen or immunogenically functional equivalent thereof and an adjuvant which is a preferential inducer of a TH1 response.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification recites *Streptococcus pnuemoniae* polysaccharide antigens 1-5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 20 22F, 23F and 33F are contemplated by the claimed invention (page 12). The specification recites *Streptococcus pnuemoniae* protein antigens pneumolysin, PsaA, PspA, PspC, CbpA or a combination of two or more of such proteins which are used in the claimed invention (page 13).

The specification is not enabling for the immunologically functional variants of *Streptococcus pnuemoniae* polysaccharide antigens 1-5, 6B, 7F, 8, (9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 20 22F, 23F and 33F nor is the specification enabling for immunologically functional variants or transmembrane deletion variants of pneumolysin, PsaA, PspA, PspC, CbpA or immunologically functional variants that are a combination of two or more such proteins. The specification only incorporates by reference the teachings of how to make and use the *Streptococcus pnuemoniae* polysaccharide antigens and *Streptococcus pnuemoniae* protein antigens of the claimed invention. The specification does not disclose, What amino acids are involved in the immunologically functional fragments or transmembrane deletion variants of pneumolysin, PspA, PspC, PsaA, glyceraldehyde-3-phosphate dehydrogenase or CbpA?

There is no guidance provided as to which amino acids can be deleted and still have the protein retain its biological function. The scope of the claims is not

commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such proteins.

The claims of the instant application are not only drawn to *Streptococcus pnuemoniae* polysaccharide antigens and *Streptococcus pnuemoniae* protein antigens but are also drawn to immunological functional equivalents or transmembrane deletion variants of these antigen. There is no guidance provided in the specification as how one would begin to choose "immunologically functional variants" or "transmembrane deletion variants". The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what immunologically functional variants or transmembrane deletion variants can be made which the retain the biological activity if the intact protein; and
- the specification provides essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to immunologically functional variants or transmembrane deletion variants having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make immunologically functional variants or transmembrane deletion variants of the claimed *Streptococcus pnuemoniae* polysaccharide antigens and *Streptococcus pnuemoniae* protein antigens in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation to is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-9 and 11 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-9 and 11 recite "immunologically functional equivalent" it is unclear as to what the applicant is referring?

4. Claims 1-9 and 11 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-9 and 11 recite "transmembrane deletion variants" it is unclear as to what the applicant is referring?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-6, 8-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blake et al *(U.S. Patent No. 5,866, 135, published February 2, 1999)* in view of Masure et al *(US. Patent No. 6,245,335, published June 12, 2001).*

Claims 1-6, 8-9 and 11 are drawn to an immunogenic composition comprising at least one *Streptococcus pneumoniae* polysaccharide antigen, at least one *Streptococcus pneumoniae* protein antigen or immunogenically functional equivalent thereof and an adjuvant which is a preferential inducer of a TH1 response.

Blake et al teach immunogenic compositions include group A streptococcal polysaccharide covalently linked to protein or liposomes to form immunogenic conjugates (see the Abstract). Blake et al teach that immunogenic compositions of the invention are conjugated to native or recombinant bacterial protein (carriers) such as tetanus toxoid, cholera toxin, diphtheria toxoid or CRM_{197} (column 3, lines 18-27). Blake et al teach that the immunogenic compositions are useful as a vaccine and may further

comprise an adjuvant such as aluminum hydroxide, aluminum phosphate, monophosphoryl lipid A, QS21 or stearyl tyrosine (column 3, lines 28-31).

Blake et al do not teach choline binding proteins.

Masure et al teach a vaccine comprising choline binding proteins (CBPs) (column 6, lines 65-67 and column 7, lines 1-8). Masure et al teach vaccines comprising CBP antigen or antigenic derivative or fragment thereof or a CBP nucleic acid vaccine that can be administered via any parenteral route including but not limited to intramuscular, intraperitoneal, intravenous and the like (column 24, lines 57-61). Masure et al suggest that criteria to consider in selecting a preferred CBP as a vaccine candidate includes testing CBP defective mutants for attenuation of virulence in animal models for bacteremia or colonization efficacy alone or in combination or coupled to a capsular polysaccharide (column 14, lines 41-46). Masure et al teach that the vaccines of the invention can be comprises an active material such as a diluent (i.e. carrier or vehicle) (column 29, lines 14-20). Masure et al teach that CBP or fragment thereof can be conjugated to an immunogenic carrier, e.g. bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH) (column 22, lines 5-8).

It would be *prima facie* obvious at the time the invention was made to add the CBP vaccines of Masure et al to the group A streptococcal polysaccharide immunogenic compositions as taught by Blake et al because Masure et al teach that one may administer the CBP vaccines in conjunction with one or more pharmaceutical compositions used for treating bacterial infection, including but no limited to antibiotics, soluble carbohydrate inhibitors of bacterial adhesion, other small molecule inhibitors of

bacterial adhesion, inhibitors of bacterial metabolism, transport or transformation, stimulators of bacterial lysis or antibacterial antibodies or vaccines directed at other bacterial antigens (column 30, lines 34-42). It would be expected barring evidence to the contrary, that the addition of the CBP vaccines of Masure et al to the group A streptococcal polysaccharide immunogenic compositions as taught by Blake et al would be effective in treating *Streptococcus pneumoniae* infections.

6. Claims 1-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuo et al *(U.S. Patent No. 5,565,204, published October 15, 1996)* in view of Masure et al *(US. Patent No. 6,245,335, published June 12, 2001).*

Claims 1-9 and 11 are drawn to an immunogenic composition comprising at least one *Streptococcus pneumoniae* polysaccharide antigen, at least one *Streptococcus pneumoniae* protein antigen or immunogenically functional equivalent thereof and an adjuvant which is a preferential inducer of a TH1 response.

Kuo et al teach a composition comprising immunogenic polysaccharide-protein conjugates and pneumolysin protein of *Streptococcus pneumoniae* (see the Abstract). Kuo et al teach that capsular polysaccharides of various pneumococcal types (for example, types 6B, 14C, 18C and 20) are used in their inventions (column 5, lines 17-28 and column 6, Example 1). Kuo et al teach that the composition may be added to immunologically acceptable diluents or carriers in the conventional manner to prepare injectable liquid solutions or suspensions (column 5, lines 45-47). Kuo et al teach that the conjugates of the invention may be bound to aluminum hydroxide, aluminum

phosphate (alum), QS-21, monophosphoryl lipid A and deacylated monophosphoryl lipid A (which induce strong TH1 responses) (column 5 lines 47-51). It is well known in the art to add protein carriers such as keyhole limpet haemocyanin (KLH), diphtheria toxoid, tetanus toxoid and protein derivative of Tuberculin (PPD) to antigens to enhance the immunogenicity of the antigen this is evidenced by *(U.S. Patent No. 6,419,932, U.S. Patent No. 4, 761, 283, U.S. Patent No. 6,224,880 and U.S. Patent No. 5,360,897).*

Kuo et al do not teach choline binding proteins.

Masure et al teach a vaccine comprising choline binding proteins (CBPs) (column 6, lines 65-67 and column 7, lines 1-8). Masure et al teach vaccines comprising CBP antigen or antigenic derivative or fragment thereof or a CBP nucleic acid vaccine that can be administered via any parenteral route including but not limited to intramuscular, intraperitoneal, intravenous and the like (column 24, lines 57-61). Masure et al suggest that criteria to consider in selecting a preferred CBP as a vaccine candidate includes testing CBP defective mutants for attenuation of virulence in animal models for bacteremia or colonization efficacy alone or in combination or coupled to a capsular polysaccharide (column 14, lines 41-46). Masure et al teach that the vaccines of the invention can be comprises an active material such as a diluent (i.e. carrier or vehicle) (column 29, lines 14-20). Masure et al teach that CBP or fragment thereof can be conjugated to an immunogenic carrier, e.g. bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH) (column 22, lines 5-8).

It would be *prima facie* obvious at the time the invention was made to add the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant

pneumolysin conjugate vaccines as taught by Kuo et al because Masure et al teach that one may administer the CBP vaccines in conjunction with one or more pharmaceutical compositions used for treating bacterial infection, including but no limited to antibiotics, soluble carbohydrate inhibitors of bacterial adhesion, other small molecule inhibitors of bacterial adhesion, inhibitors of bacterial metabolism, transport or transformation, stimulators of bacterial lysis or antibacterial antibodies or vaccines directed at other bacterial antigens (column 30, lines 34-42). It would be expected barring evidence to the contrary, that the addition of the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant pneumolysin conjugate vaccines as taught by Kuo et al would be effective in treating *Streptococcus pneumoniae* infections.

Pertinent Prior Art

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure *(Lee et al, Critical Review in Microbiology, Vol. 23, No. 2, 1997, p. 121-141 and Briles et al, Clinical Microbiology Reviews, Vol. 11, No. 4, October 1998, p. 645-657).*

Status of Claims

8. No claims are allowed.

Conclusion

9. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
August 28, 2002

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